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Novel insights into microcirculatory dysfunction in cardiogenic shock

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While cardiogenic shock (CS) is classically defined by primary cardiac dysfunction leading to impaired macrocirculatory variables—such as hypotension, reduced cardiac output (CO), and diminished left ventricular ejection fraction—growing evidence highlights the parallel and significant involvement of systemic microcirculatory dysfunction, often manifesting as tissue hypoperfusion. Indeed, most definitions of CS emphasize that it leads to tissue and end-organ hypoperfusion, evidenced in part by "signs of poor peripheral tissue perfusion." Consequently, the main clinical presentations of CS are wet-cold (~65%) and dry-cold (~30%), based on adapted Forrester perfusion/congestion profiles.

Despite advances in CS management, which emphasize rapid restoration of macrocirculatory function, mortality rates remain alarmingly high, often exceeding 40%. Notably, studies have demonstrated that up to 45% of deaths occur in patients with a normalized cardiac index, highlighting a disconnect between macrocirculatory improvement and meaningful clinical recovery.[1] This discrepancy highlights the inadequacy of solely optimizing macrocirculation, suggesting that persistent microcirculatory failure plays a critical role in driving ongoing organ dysfunction and death. While experimental data indicate an initial compensatory microvascular recruitment in the very early stages of CS,[2] recent investigations reveal that microvascular perfusion is frequently heterogeneously impaired despite restored systemic hemodynamics and that these disturbances are strongly linked to adverse outcomes. Interestingly, cerebral microcirculation appears to be protected in early experimental CS.[3]

The microcirculation (vessels ≤100 µm), comprising approximately 90% of the total vascular surface area (a far greater extent than arteries and veins of the macrocirculation), is a complex and critical system responsible for balancing tissue oxygen consumption and delivery, and thus, maintaining tissue perfusion.[3] Microcirculatory monitoring can be approached through the assessment of lactate levels—an indirect, crude, and imperfect surrogate—as well as by evaluating simple clinical signs at the bedside (Table 1). Capillary refill time (CRT) and the extent of skin mottling provide indirect yet practical information about peripheral perfusion and the adequacy of the microvascular flow. Recent advancements have enabled direct observation of the microcirculation using hand-held vital microscopy, primarily to assess the sublingual microcirculation, making precise "real-time" bedside monitoring a feasible reality.[4] Other techniques for evaluating microcirculatory function include near-infrared spectroscopy (NIRS) and skin laser Doppler imaging.

The critical prognostic importance of microcirculation in CS has been increasingly established since the early 2000s. Direct observation in numerous studies reveals severe alterations, with a 25% to nearly 50% reduction in perfused small vessel density serving as a strong and independent predictor of 30-day mortality.[5] Moreover, an increased perfused capillary density after 24 hours was significantly associated with improved survival. Notably, these microcirculatory variables exhibited no correlation with standard macrocirculatory variables, a finding reinforced by a subanalysis of the CULPRIT-SHOCK trial, which indicated that microcirculatory perfusion variables had superior prognostic value for predicting outcomes compared to macrocirculatory variables.[6]

Indirect microcirculatory assessment indicated that mottling observed at the time of admission for CS was a significant predictor of 30-day mortality.[7] Another prospective observational study corroborated these findings, demonstrating that a CRT >3 seconds at intensive care unit admission for CS was associated with worse outcomes.[8] Importantly, the predictive accuracy for this composite outcome was enhanced by combining the CardShock score with a CRT >3 seconds, achieving an area under the curve of 0.93. Recent evidence suggests that CO_2-derived variables—closely linked to microcirculatory variables—are strong prognostic markers in CS. Specifically, an average $\Delta PCO_2 \geq 9$ mm Hg and a $\Delta PCO_2/C(a–v)O_2$ ratio ≥1.5 mm Hg/mL during the first 24 hours have been significantly

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Table 1 Overview of main bedside techniques used to assess microcirculation in cardiogenic shock.

Category	Parameter/ technique	Type of measure	Main advantages	Main limitations
Biochemical	Arterial lactate	Indirect	Widely available; simple and inexpensive; correlates with severity and prognosis	Nonspecific; influenced by metabolic, hepatic, or adrenergic factors; reflects global rather than regional perfusion
Clinical (bedside)	Capillary refill time	Indirect	Easy to perform; rapid, noninvasive, and cost-effective	Semi-quantitative results, influenced by core temperature, ambient temperature, and lighting
	Skin mottling score	Indirect	Simple bedside tool; rapid, noninvasive, and cost-effective	Semi-quantitative, affected by skin color and lighting
Gas-derived indices	ΔPCO_2 (venous–arterial PCO_2 gap)	Indirect	Measurable from routine blood gases	Requires invasive sampling; influenced by CO_2 production and ventilation changes
	$\Delta PCO_2/C(a–v)O_2$ ratio	Indirect/ composite	Measurable from blood gases; enables rapid, near real-time evaluation	Complex to calculate; needs mixed venous sampling
Direct imaging	Sublingual microcirculation (handheld vital microscopy)	Direct	Provides direct visualization of capillary density and flow	Operator-dependent; frequent artifacts; agitation, or inability to cooperate can further restrict feasibility, particularly in nonintubated or hypoxemic patients; costly and not widely available
Optical techniques	Near-infrared spectroscopy	Semi-direct	Noninvasive; continuous monitoring; assesses tissue oxygenation and reactivity	Global regional measurement in sampled volume (arterioles, capillaries, and venules); influenced by the thickness of superficial tissues (eg, skin and subcutaneous fat), no direct visualization of microvascular architecture
	Skin laser Doppler imaging	Semi-direct	Quantifies superficial blood flow; allows for serial monitoring	Sensitive to motion artifacts; superficial and regional measurement; not widely available; no direct visualization of microvascular architecture

associated with increased 28-day mortality.[9] The presence of microcirculatory disturbances has also been documented in CS patients supported by venoarterial extracorporeal membrane oxygenation (VA-ECMO) and is strongly associated with their clinical course.[10]

The pathophysiology of microcirculatory dysfunction is driven by biological and cellular regulators of vascular tone and reactivity—including inflammatory mediators, endothelial signaling, and nitric oxide pathways—that impair leukocyte and erythrocyte deformability, promote their adhesion to the vessel wall, and disrupt vasomotor control, thereby compromising microvascular flow. In parallel, physical and structural determinants of flow, such as interstitial edema, venous congestion, impaired driving pressure, and capillary obstruction, alter the geometry and resistance of the microvascular network. Furthermore, impaired lymphatic contractile function may contribute to interstitial edema. In patients with advanced heart failure–related CS, reduced microcirculatory driving pressure due to increased central venous congestion–related afterload can exacerbate these alterations.[3]

Four main types of microcirculatory alterations in shock states have been defined by Ince (Figure 1).[11] Although microvascular dysfunction occurs in all forms of shock, CS is mainly characterized by a global reduction in microvascular perfusion and increased vasoconstriction, with less pronounced flow heterogeneity and endothelial activation than in sepsis; venous congestion and interstitial edema are prominent because of elevated filling pressures. In contrast, septic shock is distinguished by marked heterogeneity of microvascular flow caused by widespread vasodilation, severe endothelial injury, and functional shunting, leading to areas of both hyperperfusion and no-flow.

To date, there are few data showing benefits of any therapy on the microcirculation in CS. However, some interventions have shown promise.[3] Topical acetylcholine completely reversed microvascular blood flow changes in one study, suggesting preserved endothelial responsiveness to vasodilators. Intravenous low-dose nitroglycerin and enoximone have also demonstrated microcirculation improvement in CS. Furthermore, increasing mean arterial pressure from 65–70 to 80–85 mm Hg with norepinephrine was associated with improved microcirculation, as assessed by thenar NIRS measurements in CS. Initiation of VA-ECMO in refractory CS led to significant improvements in nearly all microcirculation variables within the first 12 hours.[11] Notably, the persistent impairment of microcirculation despite normalized macrocirculation during the initial 24 hours of VA-ECMO was associated with increased mortality. Promisingly, recent findings, using an ovine model of CS, suggest that pulsatile-flow VA-ECMO may offer benefit over standard continuous-flow VA-ECMO, as

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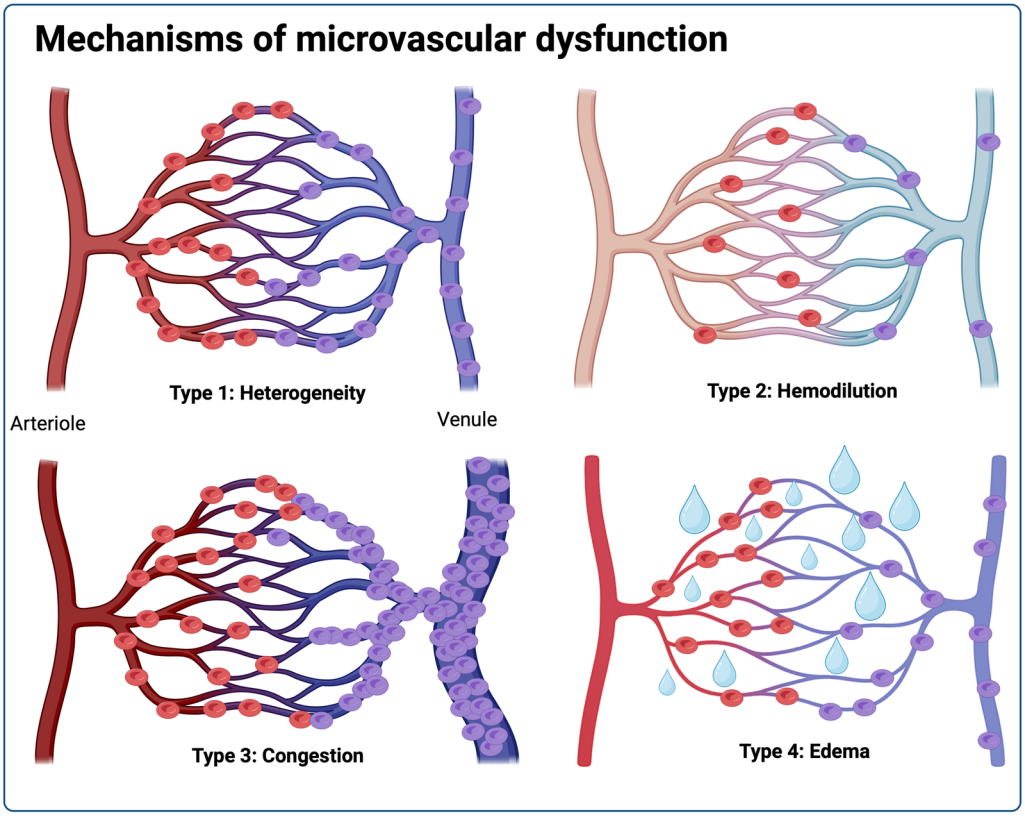

Figure 1 Mechanisms of microvascular dysfunction. Type 1: Heterogeneous perfusion of the microcirculation with poorly perfused capillaries next to well-perfused capillaries resulting in a heterogeneous oxygenation of the tissue cells. Type 2: Hemodilution with the dilution of microcirculatory blood resulting in the loss of erythrocyte-filled capillaries and increasing diffusion distance between erythrocytes in the capillaries and the tissue cells. Type 3: Congestion of microcirculatory erythrocytes flow induced by altered systemic variables (eg, increased arterial vascular resistance and/or increased venous pressures). Type 4: Tissue edema caused by capillary leak syndrome, which results in increased diffusive distance and reduced ability of the oxygen to reach the tissue cells. Red indicates well-oxygenated erythrocytes and tissue cells; purple indicates erythrocytes with reduced oxygenation and reduced tissue cell oxygenation. The figure was created with BioRender.com.

evidenced by significant improvements in sublingual microcirculation and lactate clearance during early management.[12]

The integration of microcirculatory assessment as a key endpoint in future clinical trials evaluating therapeutic interventions is urgently needed. Microcirculation has emerged as the "new frontier" in CS and should no longer be relegated to a secondary role.

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Author contributions

H.M. wrote the first draft of the manuscript. A.C., C.D., C.J., and A.M. participated in the revision of the manuscript. H.M., A.C., and C.D. participated in the revision of the figure and in the preparation of the table. All authors approved the final manuscript and consented to publication.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material. A.M. received research contracts from 4TEEN4, Roche, Sphingotec, Abbott Diagnostics, and Windtree; consultation fees from Roche, Corteria, Adrenomed, Fire, and Johnson & Johnson; honoraria for lecture from Merck, Novartis, Roche, and Bayer; is co-inventor of patent on combined therapies to treat dyspnea, owned by S-Form Pharma; and is a member of the trials committees for Secret-HF (sponsored by the French government), S-Form Pharma, 4TEEN4, Echosens, and Implicity. All other authors have no disclosures.

Artificial intelligence disclaimer

In the revision process, a few sentences underwent grammar and spelling checks and were rephrased using artificial

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intelligence to enhance clarity and readability, while preserving the original meaning and avoiding the introduction of new information.

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